Remarks

Claims 1-15, 17-23, 25 and 32-44 are pending in the subject application. By this Amendment, Applicant has amended claim 32 to attend to typographical issues and it is respectfully submitted that no new matter has been added in that regard. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-15, 17-23, 25 and 32-44 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicant gratefully acknowledges the Examiner's withdrawal of the objections to the figures, specification and claims, the double-patenting rejection over co-pending Application No. 11/597,987, and the rejection under 35 U.S.C. § 112, first and second paragraphs.

Claims 1-11, 13-15, 17-19, 21, 22, 25 and 39-41 are rejected under 35 U.S.C. § 103(a) as obvious in view of the combination of Shirley *et al.* (U.S. Published Patent Application No. 2002/0172661) and Dorin *et al.* (U.S. Patent No. 5,814,485). Claims 12, 20, 23, 24, 32-35, 37, 38 and 42-44 are rejected under 35 U.S.C. § 103(a) as obvious in view of Shirley *et al.* (U.S. Published Patent Application No. 2002/0172661) and Dorin *et al.* (U.S. Patent No. 5,814,485), and further in view of Chen *et al.* (U.S. Patent No. 6,569,420). Claim 36 is rejected under 35 U.S.C. § 103(a) as obvious in view of Shirley *et al.* (U.S. Published Patent Application No. 2002/0172661) and Dorin *et al.* (U.S. Patent No. 5,814,485), and further in view of Chen *et al.* (U.S. Patent No. 6,569,420) and further in view of Tsals *et al.* (U.S. Patent No. 5,858,001).

The Office Action indicates that Shirley *et al.* teach stabilized liquid formulations of IFN-β, including recombinant IFN-β in a solution with a buffer, wherein the buffer is in an amount sufficient to maintain the pH of the composition within plus or minus 0.5 units of a specified pH, wherein the specified pH is about 3.0 to about 5.0, and wherein the IFN-β concentration can range from 0.01 mg/ml to 20 mg/ml (10 μg/ml - 20,000 μg/ml). The Office Action also indicates that Shirley *et al.* teach numerous suitable buffers, including acetate buffer at a concentration range of 1 - 30 mM and that this composition can further comprise a "tonicifying agent" such as mannitol. Finally, Shirley *et al.* is cited as teaching inclusion of bacteriostatic agents. The Office Action alleges that Dorin *et al.* teach compositions comprising IFN-β, and teach that these IFN-β formulations can comprise 2-hydroxypropyl-beta-cyclodextrin, and also teach that inclusion of 2-hydroxypropyl-beta-

cyclodextrin is useful as a protectant because it helps reduce the physical and chemical alterations to IFN-β polypeptides, such as oxidation. The Office Action also asserts that the Dorin *et al.* patent teaches that 2-hydroxypropyl-beta-cyclodextrin helps prevent unwanted aggregation, chemical linkage, oxidation, and degradation of IFN-β. Applicant further notes that the Office Action asserts (at page 7) that "it is noted that a person of ordinary skill in the art would have the motivation, and the ability, to optimize the concentrations or amounts of various reagents in order to create the most effectively stabilized formulation. M.P.E.P 2144.05 states: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 U.S.P.Q. 223, 235, (C.C.P.A. 1955)." Applicant respectfully asserts that the claimed invention is not obvious over the cited references and traverses the rejection. The Office Action also relies on Chen *et al.* for the teaching of adding yet another protectant (methionine) to the IFN-β formulations provided by the combination of Shirley *et al.* and Dorin *et al.* and Tsal *et al.* for teachings related to autoinjectors.

In the Final Rejection dated January 25, 2010, the Office Action argues that Dorin *et al.* teach that HPBCD is an art recognized protectant of polypeptides, helps prevent oxidation, aggregation, chemical linkage and degradation of polypeptides. The Office Action further argues that Dorin *et al.* teach "too much amorphous protectant will hinder efficient lyophilization, and too little will reduce the shelf life of the lyophilized product" (column 13, lines 29-31). Therefore, it would be expected that determining the most effective amount of HPBCD would be critical in the formulation of a pharmacologically effective IFN formulation, and because HPBCD is indeed a result effective variable, it would be obvious to optimize the concentration or amount via routine experimentation.

Applicant, again, respectfully traverses the rejection and arguments set forth in the Office Action. Applicant notes that neither Dorin *et al.* nor Shirley *et al.* provide any teaching as to the amounts of EDTA or HPBCD that are to be used as a protectant in the formulations taught by either reference. Indeed, Dorin *et al.* is a reference directed to methods of making IFN-β in *E. coli* cells, see, for example, the claims and examples, and makes only passing reference to IFN-β formulations at columns 12-14. The Dorin *et al.* reference also fails to provide any direction as to the amount of HPBCD to be added to such formulations. Shirley *et al.*, likewise, fail to provide any direction to the amounts of EDTA that are to be added to IFN-β formulations as a stabilizer. As noted previously,

additional guidance regarding obviousness determinations has been provided by the Court of Appeals for the Federal Circuit in *Bayer Schering Pharma AG. v. Barr Lab., Inc.*, 575 F.3d 1341, 1347, 91 USPQ2d 1565, 72-73 (Fed. Cir. 2009). There it is stated:

> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell,* 853 F.2d at 903. This is another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble,* 566 F.3d at 996; *Kubin,* 561 F.3d at 1359. It is also consistent with our interpretation that KSR requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.,* 520 F.3d 1358, 1364 (Fed.Cir.2008).
>
> Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell,* 853 F.2d at 903. This expresses the same idea as the *KSR* requirement that the identified solutions be "predictable." 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble,* 566 F.3d at 996-97; *Kubin,* 561 F.3d at 1359-60.

In this case, Applicant submits that the cited prior art references would require one of ordinary skill in the art to try all possibilities in a field unreduced by the prior art and/or as vague prior art that does not guide an inventor to a particular solution. As noted above, neither reference provides any guidance as to an amount of HPBCD or EDTA that are to be used as stabilizers; thus, one skilled in the art would have been required to both try all possibilities regarding concentrations of HPBCD that were to be used for stabilizing IFN-β formulations since both references are silent as to the amount of such a compound that should be used to stabilize IFN-β formulations and there was no guidance in Shirley *et al.* as to the amounts of EDTA that could be used in a similar fashion within the teachings of that reference.

The Office Action further argues that it would have been obvious to add a second and/or third antioxidant/protectant, such as HPBCD and methionine to the IFN-β formulation of Shirley *et al.* on the basis that one skilled in the art would have recognized that anti-oxidants, such as HPBCD and EDTA are result-effective variables that are effective for the same purpose, that one would know that they are interchangeable, or alternatively, would suspect that a formulation comprising both EDTA and HPBCD would be effectively protected from oxidation, relying upon *In re Kerkhoven* for the premise that it is *prima facie* obvious to combine two compositions taught by the prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose. Applicant respectfully disagrees and traverses the rejection.

Applicant, again, submits that the combination of references relied upon to reject the presently claimed invention does not teach or suggest the use of more than one anti-oxidant (let alone three structurally dissimilar and unrelated anti-oxidants) within the composition containing IFN-β and reliance on *In re Kerkhoven* fails to remedy this defect. Both this application (see page 3, lines 18-24) and Shirley *et al.* (at paragraph 6) indicate:

> The stabilization of polypeptides in pharmaceutical compositions remains an area in which trial and error plays a major role (reviewed by *Wang (1999) Int. J. Pharm. 185:129-188; Wang and Hanson (1988) J. Parenteral Sci. Tech. 42:S3-S26*). Excipients that are added to polypeptide pharmaceutical formulations to increase their stability include buffers, sugars, surfactants, amino acids, polyethylene glycols, and polymers, but the stabilizing effects of these chemical additives vary depending on the protein.

Thus, it is clear that the effects of various excipients in the preparation of pharmaceutical compositions comprising IFN-β was considered unpredictable and there is no evidence of record that teaches or suggests that one skilled in the art would have recognized EDTA and HPBCD as "interchangeable".

Regarding the argument that one of ordinary skill in the art would suspect that a formulation comprising both EDTA and HPBCD would be effectively protected from oxidation, Applicant notes that Dorin *et al.* state that "Too much amorphous protectant [*i.e.*, the combined formulation of EDTA and cyclodextrin or EDTA, cyclodextrin and methionine as argued in the Office Action under the *In re Kerkhoven* premise] will hinder efficient lyophilization, and too little will reduce the shelf

life of lyophilized product" (see column 13, lines 29-31). Thus, combining EDTA and HPBCD (or EDTA, HPBCD and methionine in the rejection combing Shirley *et al.*, Dorin *et al.* and Chen *et al.*) would most likely have adversely affected the properties of the IFN-β formulation because combining EDTA and HPBCD (or EDTA, HPBCD and methionine), particularly without the benefit of any guidance regarding the amounts of these agents that should be added to IFN-β formulations, would have been expected to result in too much amorphous protectant within the formulations and an adverse effect on the performance of the formulations that one would arrive at when combining all these protectants. Accordingly, it is respectfully submitted that the claimed invention is not obvious over the combined teachings of Shirley *et al.* in view of Dorin *et al.*, Shirley *et al.* and Dorin *et al.* in view of Chen *et al.*, or Shirley *et al.*, Dorin *et al.* and Chen *et al.* in view of Tsals *et al.* and reconsideration and withdrawal of these rejections is respectfully requested.

Claims 1-15, 17-23, 25, 32-37 and 38-44 are provisionally rejected for obviousness-type double patenting over claims 1, 3, 5-8, 10-16, 18-33 and 34-39 of co-pending application 10/554,602, in view of Dorin *et al.* Applicant respectfully asserts that the claims, as amended herein, are not obvious over the claims of the cited application.

As noted above, there is no evidence of record that teaches or suggests that one skilled in the art would have recognized methionine and HPBCD as "interchangeable" as it appears that the effects of various excipients in the preparation of pharmaceutical compositions comprising IFN-β was considered unpredictable at the time the instant invention was made (see, for example, see page 3, lines 18-24 of this application and Shirley *et al.* at paragraph 6, "The stabilization of polypeptides in pharmaceutical compositions remains an area in which trial and error plays a major role.").

Regarding the argument that one of ordinary skill in the art would suspect that a formulation comprising both methionine and HPBCD would be effectively protected from oxidation, Applicant notes that Dorin *et al.* state that "Too much amorphous protectant [*i.e.*, the combined formulation of methionine and cyclodextrin as argued in the Office Action under what appears to be an *In re Kerkhoven* premise] will hinder efficient lyophilization, and too little will reduce the shelf life of lyophilized product" (see column 13, lines 29-31). Thus, combining methionine and HPBCD would most likely have adversely affected the properties of the IFN-β formulation because combining methionine and HPBCD, particularly without the benefit of any guidance regarding the amounts of

these agents that should be added to IFN-β formulations, would have been expected to result in too much amorphous protectant within the formulations which would have been expected to adversely affect the properties of the formulation. Accordingly, it is respectfully submitted that the claimed invention is not obvious over the '602 application in view of Dorin *et al.* and reconsideration and withdrawal of the rejection is respectfully requested.

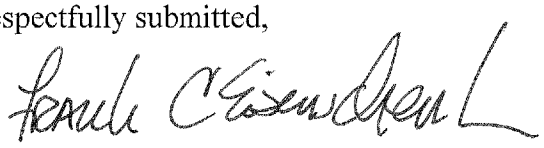
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position. Applicant expressly reserves the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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